Gene Correction of Autologous Hematopoietic Stem Cells in Artemis Deficient SCID

Grant Award Details

Gene Correction of Autologous Hematopoietic Stem Cells in Artemis Deficient SCID

Grant Type: Early Translational III

Grant Number: TR3-05535

Project Objective: The ultimate objective of this study is to generate the necessary conditions for gene-corrected autologous hematopoietic stem cell transplantation (HSCT) in children with Artemis-deficient severe combined immunodeficiency (SCID-A).
They will conduct studies to demonstrate in vitro and in vivo correction of Artemis-deficient human hematopoietic stem cells (CD34+HSC) by transducing these cells with a lentiviral vector containing the human Artemis gene with the human Artemis promoter (AProArt). The strategy for accomplishing this is to collect and cryopreserve human Artemis-
deficient CD34+ stem cells. They have collected cord blood and CD34+ bone marrow stem cells from two Artemis deficient SCID patients and have set up a collaboration with Dr. Harry Malech at NIAID
-NIH to collect cytokine mobilized peripheral blood stem cells (PBSC)from Artemis-deficient SCID adults who received an allogeneic
transplant many years ago without myeloablative conditioning and who have reconstituted T but not B cell immunity and have <1% donor CD34+ stem cells in their marrow and blood.
The CD34+ cells from these patients should be >99% host-derived,and thus, Artemis-deficient.

Investigator:

Name:	Morton Cowan
Institution:	University of California, San Francisco
Type:	PI

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Name:	Jennifer Puck
Institution:	University of California, San Francisco
Type:	Co-PI

Disease Focus: Immune Disease, Pediatrics

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $3,931,662

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE (Year 4)

View Report

Grant Application Details

Application Title: Gene Correction of Autologous Hematopoietic Stem Cells in Artemis Deficient SCID

Public Abstract: Artemis is a chemical in all cells in the body that is essential for the normal development of the immune system and repairing damaged DNA. Artemis deficiency (AD) causes Severe Combined Immunodeficiency (SCID-A), a “bubble baby” syndrome associated with increased sensitivity to radiation and chemotherapy. SCID-A is hard to treat with a bone marrow stem cell (SC) transplant from another person due to rejection, reactions from the graft, and toxicity from high dose chemotherapy. Gene corrected (GC) patient’s SC will minimize the risks and cure SCID-A. Our objectives are to 1) Maximize engraftment of GC SC by opening marrow space without using high dose chemotherapy; 2) Assess harmful effects after gene correction of mouse and human SC by developing safety testing suitable for clinical trial use; and 3) Demonstrate that GC human SC from SCID-A patients correct the defective immunity in animal and cell models. Using an AD mouse model we will open marrow spaces by using a genetically engineered drug which targets SC (yr 1) ± an agent which blocks marrow SC attachment (yr 2), and find the minimal effective dose of chemotherapy (year 3). We will test for toxicity using several approaches (yrs 1-3). AD SC will be corrected with our lentiviral vector (AProArt) using clinical trial conditions and cultured on special cells that support SC growth into immune cells. Immunodeficient mice will be injected with GC human SC and human SC differentiation into immune cells evaluated (yrs 2-3).

Statement of Benefit to California:	Artemis deficient Severe Combined Immunodeficiency Disease (SCID-A) results in T-B-NK+ SCID with increased sensitivity to alkylator chemotherapy, and accounts for ~10% of all SCID patients. Athabascan-speaking Native Americans have a very high incidence of SCID-A (2/5000 births) and affected children from other states are sent to [redacted] for curative treatment. California has been among the leading states in instituting newborn screening for SCID and [redacted] is one of the main referring hospitals for these newly-diagnosed babies. In the first year of newborn screening, 8 babies with SCID were born in CA. Currently, the only cure for this otherwise fatal disease is an allogeneic hematopoietic stem cell (HSC) transplant in which high dose alkylator chemotherapy is often necessary to overcome graft rejection and open sufficient bone marrow niches to reconstitute both T and B cell immunity. Successful gene correction of SCID-A will eliminate the need for high dose alkylator chemotherapy and significantly reduce the mortality of HSC transplantation and cost of lengthy hospitalization and long term care for the late effects due to alkylator use in these newborn babies. The approaches that are developed in this project for successful gene therapy without using high dose chemotherapy will benefit all children in California (and elsewhere) with a variety of genetic diseases who may benefit from curative cellular therapy.
